Alicaforsen in the treatment of pouchitis

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Abstract: Alicaforsen is a 20-base antisense oligonucleotide inhibiting ICAM-1 production, which is an important adhesion molecule involved in leukocyte migration and trafficking to the site of inflammation. Hitherto, alicaforsen has been granted orphan drug designation and is prescribed as an unlicensed medicine in accordance with international regulation for the treatment of pouchitis and left-sided ulcerative colitis. Given the positive results evolving from one open-label trial and one case series in patients with chronic refractory pouchitis, US FDA has agreed to a rolling submission for a license application for the treatment of pouchitis, which has been recently initiated. Whether alicaforsen leads to higher endoscopic and clinical remission rates as placebo and whether the response can be maintained in the long-term in larger studies is yet unknown. An ongoing multicenter international Phase III trial will definitely address these unanswered questions.

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Alicaforsen, an Antisense Inhibitor of ICAM-1, as Treatment for Left-Sided Ulcerative Colitis and Ulcerative Proctitis

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ABSTRACT

Background and aims: Data about the efficacy of the intercellular adhesion molecule-1 (ICAM-1) antisense oligonucleotide termed alicaforsen in ulcerative colitis (UC) is inconsistent. (1) We have recently suggested a role for alicaforsen in the treatment of refractory pouchitis. (2) This case series on 12 UC patients reports on the efficacy in left-sided UC and proctitis. Methods: We performed a retrospective analysis on all patients who had received at least one dose of Alicaforsen at six referral centers in Switzerland. We assessed the drug`s efficacy in patients treated for left-sided UC and proctitis by comparing clinical and/or – if applicable – endoscopic disease activity scores before and after treatment. Results: 12 patients were treated for left-sided UC or proctitis. 11 patients received a full 6-week course of a once-daily 240mg alicaforsen enema formulation, in 1 patient treatment was early discontinued due to lack of efficacy. Off-label Alicaforsen was chosen in the majority of patients in order to defer systemic treatment despite a severe disease course (6/12, 50.0%). Clinical disease activity measured by the partial Mayo score and a 6-point symptom score (adapted from the Mayo Score) was significantly reduced after treatment (6.0 vs. 2.4, p=0.011 and 3.7 vs. 1.4, p=0.008, respectively). Fecal calprotectin was considerably reduced after alicaforsen treatment (484.4 vs. 179.5µg/g), however the difference did not reach statistical significance (p=0.063). Clinical improvement was achieved in 10 out of the 12 patients (83.3%). However in 7 of those, a relapse occurred (70%). Median duration of clinical response was 18.0 weeks (range 1-112). Three patients showed an ongoing response of more than 9 months. No adverse events were reported. Conclusions: A 6-week course of Alicaforsen as enema formulation seemed to be safe and efficacious in inducing clinical improvement in patients with left-sided UC and proctitis. Prolonged response was observed in many, but not all patients.

INTRODUCTION

Gut-selective immunosuppressive agents such as Vedolizumab or Mongersen are very promising given their similar efficacy, but lower rates of side-effects compared to anti-TNF treatment. (3-5) Infectious complications of anti-TNF remain a significant concern in clinical treatment decision and development of highly gut-selective therapies interacting with gut inflammation but preserving systemic immune response have become a priority in the field of inflammatory bowel disease (IBD) research. (6) Such therapies take advantage of the specific molecular interactions in leukocyte trafficking. (7) Leukocyte trafficking is a multistep process involving both the -immune and the endothelial cell, which enables direction of leukocytes to the site of inflammation: leukocytes tether, get activated, adhere to the endothelium and finally migrate through the endothelial layer. For this sequence, interaction between proteins on the surface of leukocytes and their corresponding ligands are crucial: integrins are expressed on immune cells and bind to their counterpart molecules of the immunoglobulin superfamily on endothelial cells. The latter consist of intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule (VCAM) or mucosal vascular addressin cell adhesion molecule (MAdCAM). While MAdCAM interacts with $\alpha 4\beta 7$ integrin, which is therefore causative for the efficacy of vedolizumab, ICAM-1 is a transmembrane glycoprotein expressed on the surface of intestinal epithelial cells and vascular endothelial cells that binds to $\beta 2$ integrins and therefore promotes firm adhesion of leukocytes to the endothelium. (8, 9) Expression of ICAM-1 is upregulated by TNFα, interleukin-1, interferon-γ (IFNγ) and/or lipopolysaccharide (LPS). (10) Inflammation triggered by those factors (such as in IBD) results in an increased leukocyte adhesion and trafficking. Several studies suggest that an increased expression of ICAM-1 is a part of the pathology of IBD, (11-16) which has led to the idea of blocking the ICAM-1 pathway in IBD treatment.

Alicaforsen is a human ICAM-1 antisense oligonucleotide, which blocks ICAM-1 production by complementary hybridization to the messenger ribonucleic acid (mRNA) of the target gene resulting in hydrolysis of the created deoxyribonucleic acid-ribonucleic acid (DNA-RNA) complex by a RNase enzyme. (17) While the systemic administration of Alicaforsen in Crohn`s

disease (CD) was not efficacious (18-20) and two randomized-controlled trials evaluating the role of topical alicaforsen in UC failed to show short-term efficacy, patients treated with the enema formulation seemed to have a long-term benefit. (1, 21, 22) This has led to the hypothesis of a disease-modifying effect. In addition, two small open label studies evaluating the role of Alicaforsen in chronic pouchitis have shown promising results even in difficult to treat cases. (2, 23)

Taken together, there might be a role for topical Alicaforsen in the treatment of chronic pouchitis and left-sided UC. This case series analyzes the efficacy and safety of a 6-week course of Alicaforsen as enema formulation in the treatment of left-sided UC and ulcerative proctitis.

METHODS

Subjects

We performed a retrospective analysis on all patients who had received at least one dose of Alicaforsen at six IBD referral centers in Switzerland with at least one follow-up visit (University Hospital Zurich, Triemli Hospital Zurich, Gastrozentrum Hirslanden Zurich, Tiefenauspital Bern, Kantonsspital St. Gallen, and the outpatient clinic MagenDarm AG Basel). Patient information was extracted from each patient's chart. Patients were excluded if they were under the age of 16. Diagnosis of underlying IBD had to be established based on clinical course, endoscopy and histology according to current international guidelines. As Alicaforsen has currently an off-label status in Switzerland, approval from the patient`s health care insurance for reimbursement and from the Swiss Agency for Therapeutic Products (SwissMedic) was needed prior to the first administration. For a detailed outcome analysis, only patients treated for left-sided UC and/or ulcerative proctitis were included. All patients were currently enrolled in the Swiss IBD Cohort Study, which an ethical approval is available for. Written informed consent had been obtained from every patient.

Data collection

The following data was collected from individual`s patient charts: patient demographics (sex, age, smoking status), prior medical and surgical history, prior therapies and current co-medications, disease characteristics (age at disease onset, disease localization, disease course), laboratory parameters (full blood count, C-reactive protein (CRP), BSR, fecal calprotectin), endoscopic findings (if applicable), symptom severity (stool frequency, rectal bleeding). In order to grade clinical disease activity we used the partial Mayo Score and a 6-point symptom score adapted from the Mayo Score, (24) which both had been used in UC studies. (25) In addition, disease activity was globally assessed by the treating physician based on his interpretation of clinical, endoscopic and histological findings ranging from remission to mild, moderate, and severe activity. If applicable, total Mayo score was calculated. We further collected all data on the use of Alicaforsen including exact indication, dosage, duration and side-effects. In order to evaluate the efficacy of Alicaforsen, we used the following definitions

of clinical improvement in accordance to our prior study evaluating alicaforsen in chronic pouchitis: (2)

Presence of all of the following criteria:

- Reduction of stool frequency
- Reduction of partial Mayo Score and/or 6-point symptom score
- Responsible clinician considers disease course as improvement in synopsis of clinical symptoms, quality of life and – if applicable – endoscopic findings.

Last visit within 3 months before initiation of Alicaforsen was taken as pre-treatment evaluation. Endoscopic findings were excluded if endoscopy was performed >1 year before baseline assessment. Re-assessment of disease activity had to be done within 6 months after treatment initiation. Relapse was defined as increasing clinical and/or endoscopic disease activity after a period of clinical improvement. Duration from clinical improvement to first relapse was recorded for Kaplan Meier analysis.

Statistical analysis

For all statistical analyses, SPSS version 22.0.0 (2013 SPSS Science, Inc., Chicago, IL) was used. Metric data is shown as medians with total range. Categorical data are summarized as the percentage of the group total. For outcome analysis (before vs. after), Wilcoxon signed rank test was used for ordinary data and for continuous variables as they showed a non-normal distribution. For calculation of the clinical improvement-to-relapse-time, a Kaplan Meier analysis was performed. A two-sided p-value of <0.05 was regarded as statistically significant.

RESULTS

Overview of patients treated with alicaforsen

We identified 30 patients with at least one-follow-up visit, who had received at least one dose of Alicaforsen. Median age was 37.5 years (17.0-69.5) when treatment with Alicaforsen was initiated. 29 patients suffered from UC, while 1 patient had been diagnosed with CD. Median age at IBD diagnosis was 24.4 years (7.5-59.0). At the time of initiation of Alicaforsen, median duration of IBD was 12.8 years (1.5-43.2). Indication for Alicaforsen treatment was as follows: 12 patients were being treated for left-sided UC or proctitis, while 16 were treated for chronic pouchitis after proctocolectomy, 1 patient was treated for CD proctitis and 1 patient for ischemic pouchitis. In only 2 patients (1 treated for CD proctitis and 1 for left-sided UC colitis), Alicaforsen was discontinued early after 10 days and 5 weeks, respectively. In both cases, lack of efficacy was the reason for early discontinuation. 24 of the 30 patients showed an improvement of the underlying condition based on physician`s global assessment. 19 of those patients experienced a relapse with a median duration from improvement to relapse of 12 weeks (1-112). No adverse events were reported. Results of those patients treated for chronic refractory pouchitis have been published in a prior case series. (2) Demographic data of all patients are depicted in **Table 1**. **Supplementary Table 1** shows a synopsis of all 30 patients treated with at least one dose of alicaforsen.

Patients treated for left-sided UC/proctitis

The 12 patients treated for left-sided UC or proctitis had a median age of 36.7 years (range 17.0-69.5). 5 patients were female (41.7%). Median age at UC diagnosis was 25.0 years (7.5-59.0). Median duration of UC at initiation of Alicaforsen treatment was 11.8 years (1.5-14.8). 7 of the 12 patients (58.3%) had left sided UC (Montreal Classification E2), while the remaining 5 patients (41.7%) suffered from ulcerative proctitis (Montreal Classification E1). **Table 2** depicts demographic data and disease characteristics of those 12 patients treated for left-sided UC/proctitis. No history of C. difficile infection was reported, while 1 patient previously had had a CMV colitis. 4 patients were prior smokers. One patient with proctitis had previously undergone left-sided hemicolectomy due to sigma perforation. 11 of the 12 patients (91.7%) received a full 6-week course of 240mg Alicaforsen once-daily as enema formulation, while in

1 patient Alicaforsen was early discontinued after 5 weeks due to lack of efficacy. No adverse events were reported. Indication for the off-label use of Alicaforsen were: to defer systemic treatment despite a severe disease course (6/12, 50.0%), malcompliance with oral medications (1/12, 8.3%), severe course despite prior topical steroids and immunosuppressive agents (1/12, 8.3%), pregnancy with 5-ASA intolerance (1/12, 8.3%), and left sided UC before switch of anti-TNF (2/12, 16.7%). Physician`s global assessment revealed a moderate-to-severe disease activity in 10 out of 12 patients (83.3%). Only two patients were assessed to have mild disease. No patient was in remission. At baseline, median Mayo Score was 9.0 (4.0-11.0), partial Mayo Score was 7.0 (1.0-8.0) and 6-point symptom score was 4.5 (0.0-5.0). Patients reported a median of 7 stools per day (1-10). For a comprehensive synopsis on each individual patient, we refer to the **supplementary tables 2 and 3.**

Overall study outcome

Median follow-up (time from treatment initiation to first follow-up visit) was 3.0 months (1.6 - 5.5 months). 6 of the 12 patients were treated with Alicaforsen alone, while the remaining 6 patients received concomitant therapy: 1 patient was treated with overlapping prednisone, which was tapered within the first 2 weeks, 1 patient was treated with overlapping prednisone for 2 weeks and ongoing therapy with azathioprine and 5-ASA, 1 patient was concomitantly treated with ongoing topical budesonide and 5-ASA, 1 patient continued with oral and topical 5-ASA, 1 patient continued with oral 5-ASA, azathioprine and certolizumab pegol, and 1 patient continued with infliximab. Clinical disease activity was significantly reduced at the first follow-up visit. Mean partial Mayo score and the 6-point symptom score (adapted from Mayo Score) showed a decrease from 6.0 to 2.4 and from 3.7 to 1.4, respectively ($p=0.011$ and $p=0.008$). Total Mayo score and stool frequency both showed a relevant decrease from 8.6 to 5.3 and from 6.2 to 4.0, however differences were not statistically significant ($p=0.092$ and $p=0.074$). In 5 patients no follow-up endoscopy was performed. Fecal calprotectin as a marker of intestinal disease activity was considerably reduced after Alicaforsen treatment (mean 484.4 vs. 179.5µg/g), however the difference did not reach statistical significance ($p=0.063$), as a

complete set (both pre- and post-treatment) was available only for 7 of the 12 patients. Similar results were seen, if those patients having mild disease at treatment initiation were excluded – as those are less likely to benefit from Alicaforsen: Mayo Score 9.5 vs. 6.8 (p=0.197), partial Mayo Score 6.8 vs. 2.9 (p=0.020), 6-point symptom score 4.2 vs. 1.7 (p=0.013), stool frequency 7.15 vs. 4.6 stools/day (p=0.110) and fecal calprotectin 554.8ug/g vs. 208.0 (p= 0.075).

Clinical improvement was achieved in 10 out of the 12 patients (83.3%). Median duration of clinical response was 18.0 weeks (1.0-112.0). In 7 of the 10 patients with clinical improvement, a relapse was observed (70%). Median time from response to relapse was 6 weeks (1.0-112.0). Three patients showed a sustained clinical response; in those patients, duration of clinical response was 36, 69 and 73 weeks, respectively. **Figure 1 A-D** shows clinical disease activity (Partial Mayo score (A), 6-point symptom scale (B), Mayo score (C) and fecal calprotectin (D)) at baseline versus at first follow-up visit after treatment. **Figure 2** shows Kaplan-Meier analysis of duration of clinical response.

DISCUSSION

This retrospective case series analyzes the efficacy and safety of Alicaforsen as enema formulation in the treatment of left-sided UC and ulcerative proctitis in 12 patients in Switzerland. After a median of 3 months, patients treated with a 6-week course of Alicaforsen showed a significant reduction in clinical disease activity (as assessed by partial Mayo score and 6-point symptom score). We found that 10 out of 12 patients showed a clinical response to Alicaforsen; however, in 7 of those (70%) a relapse occurred. Median duration of clinical

response was 18.0 weeks. In three patients with a sustained response, duration of clinical improvement was more than 9 months.

Data on the potential role of Alicaforsen in IBD treatment is inconsistent. In CD, randomized-controlled trials with intravenous/subcutaneous drug formulation failed to show short-term efficacy of Alicaforsen (at week 12 and 14, respectively), although post-hoc analysis suggested higher response rates with higher drug concentrations. (18-20, 26) In left-sided UC, In a small open label study Miner at al. could demonstrated that Alicaforsen enema provides local treatment without meaningful systemic exposure; at week 6, disease activity index was reduced by 46% with 12 out of 15 patients having achieved clinical improvement. (27) Two larger randomized-controlled trials by van Deventer and Minder failed to show (short-term) efficacy of the enema formulation: disease activity at week 6 was not significantly reduced compared to placebo and mesalazine, respectively. (1, 21) Nonetheless, a prolonged clinical response was observed in both trials with a significant reduction in disease activity at week 18 and 30 compared to placebo (51 vs. 18% and 50 vs. 11%) and a significant longer duration of response compared to mesalazine (146 vs. 54 days). In a smaller randomized-controlled trial van Deventer et al. showed both a short-term and long-term benefit from Alicaforsen enema treatment: disease activity was reduced by 78% at day 29 and by 68% at 3 month compared to a placebo response of 28% and 11.5%, respectively. (28) Given the fact, that the half-life period of Alicaforsen is only 24 hours, these findings have led to the concept of a disease-modifying effect.

Our results with a clear and fast reduction of clinical disease activity (Mayo score –27%, partial Mayo score –60%, and 6-point symptom score –62%) are consistent with the open label study by Miner et al. and the small randomized-controlled trial by van Deventer. (27, 28) The clinical improvement rate of 83.3% (10 out of 12) is comparable to that of Miner at al. (clinical improvement in 12/15 patients (80%)). (27) These findings highlight the potential short-term benefit from a single 6-week course of Alicaforsen. However, 7 of the 10 patients with initial clinical improvement had a clinical relapse. The median duration of response of 18.0 weeks

(corresponding to 126 days) is nearly as high as indicated by Miner et al (146 days). (21) Four patients had a response of more than 9 months, 3 of them without any further IBD treatment, the remaining patient with ongoing topical and oral 5-ASA only. 4 patients had a clinical improvement of less than or equal to 8 weeks. It remains to be determined, which patients show a prolonged response after a single 6-week course of Alicaforsen and which patients do not. Repeated treatment courses and/or maintenance therapy may lead to longer response rates as it has been reported in the case series regarding Alicaforsen in the treatment of chronic pouchitis. (2) So far, none of our patients had received a second trial due to the off-label use of Alicaforsen and the difficulty of reimbursement by the Swiss health care insurances.

No serious adverse events were reported underlying the safety of the topical applied drug. In addition, topical delivery was well tolerated and none of the patients showed malcompliance. to

A limitation of our case series certainly is its retrospective nature and subsequently the lack of controls and blinding. 6 patients (50%) received concomitant treatment. However, 4 of the 6 patients only continued the medications, which they had been on for a long time. In 2 patients, oral prednisone was tapered. The tapering of the steroids was well tolerated under Alicaforsen treatment. The two patients with prior and ongoing anti-TNF exposure did show the worst outcome (1 patient with no response, 1 patient with a relapse after 1 week). The concern that anti-TNF co-medication may have affected the study outcome positively, seems to be negligible. In contrast, failure to respond to anti-TNF may be a negative predictor for treatment success with Alicaforsen.

The presented results are based on the partial Mayo score and the 6-point symptom score (adapted from the Mayo score). Full Mayo score was only applied in 7 of the 12 patients due to the lack of follow-up endoscopies. However, both the partial score and the symptom score have been previously validated for UC. (25) The study population was limited due to the off-

label drug use and difficulty in reimbursement of the study drug from health care insurances. However, the study sample was nearly equal to that of the open label study by Miner et al. (27)

In conclusion, a 6-week course of Alicaforsen was safe and showed seom efficacy in inducing clinical improvement in left-sided UC and proctitis, and is – at least in some patients – sufficient for maintaining clinical response. Further studies with more patients are needed to answer the question, which patients may benefit from a single 6-week course and which patients may need repeated treatment courses.

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Nr	Sex	Age in years	IBD	Age at diagnosis	Indication for treatment	Duration of treatment (in weeks)	Early discontinuation	Response	Duration	Relapse	Ongoing response	ADE
1	f	44.2	UC	38.6	Left-sided Colitis	6	No	Yes	112	Yes	No	No
2	m	36.3	UC	23.7	Left-sided Colitis	6	No	Yes	18	Yes	No	No
3	m	21.2	UC	7.5	Proctitis	6	No	Yes	73+	No	Yes (73 weeks +)	No
4	m	17.0	UC	15.5	Proctitis	6	No	Yes	69+	No	Yes (69 weeks +)	No
5	f	37.0	UC	22.5	Left-sided Colitis	6	No	Yes	8	Yes	No	No
6	f	46.0	UC	33.2	Left-sided Colitis	6	No	Yes	1	Yes	No	No
7	F	30.6	UC	25.0	Proctitis	6	No	No				No
8	F	28.5	UC	25.7	Proctocolitis	6	No	Yes	1	Yes	No	No
9	NA	NA	UC	NA	Proctitis	6	No	Yes	NA	Yes	No	No
10[1]	m	57.6	UC	42.9	Pouchitis	6	No	Yes	3	Yes	No	No
11[1]	f	59.8	UC	38.0	Pouchitis	6	No	Yes	12	Yes	No	No
12[1]	m	24.5	UC	15.3	Pouchitis	6	No	Yes	12	Yes	No	No
13[1]	m	38.0	UC	29.8	Pouchitis	6	No	Yes	12	Yes	No	No
14[1]	f	35.5	UC	11.4	Pouchitis	6	No	Yes	14+	No	Yes (14 weeks +)	No
15[1]	f	64.5	UC	57.7	Pouchitis	6	No	Yes	7	Yes	No	No
16[1]	m	28.0	UC	20.0	Pouchitis	2X6	No	Yes	40	Yes	No	No
17[1]	f	54.3	UC	40.2	Pouchitis	6	No	Yes	91	Yes	No	No

18[1]	m	69.5	UC	44.6	Pouchitis	6	No	No				No
19[1, 2]	m	21.5	UC	16.7	Pouchitis	6	No	Yes	16	Yes	No	No
20[1]	m	23.7	UC	17.6	Pouchitis	6	No	Yes	13+	No	Yes (13 weeks +)	No
21[1]	f	49.5	UC	31.2	Pouchitis	6	No	Yes	28	Yes	No	No
22[1]	m	32.4	UC	13.6	Pouchitis	6	No	No				No
23	f	53.9	UC	NA	Ischemic pouchitis	6	No	No				No
24	f	28.9	CD	11.1	Proctitis	1.5	Yes (after 10d due to lack of efficacy)	No				No
25	f	28.6	UC	18.4	Pouchitis	6	No	Yes	12	Yes	No	No
26	m	67.5	UC	59.0	Proctitis	6	No	Yes	36+	No	Yes (36 weeks +)	No
27	m	66.0	UC	22.9	Pouchitis	6	No	Yes	12	Yes	No	No
28	m	58.6	UC	37.3	Pouchitis	6	No	Yes	4	Yes	No	No
29	m	34.0	UC	22.1	Left-sided Colitis	6	No	Yes	4	Yes	No	No
30	m	69.5	UC	54.8	Left-sided Colitis	5	Yes (after 5 weeks due to lack of efficacy)	No				No

Supplementary Table 1: All patients treated with Alicaforsen. [1] Patients 10-22 have been previously described in the case series by Greuter et al. [2] Patient 19 was re-treated with alicaforsen after first clinical improvement and relapse; patient 19 showed a second clinical improvement for 12 weeks.

Nr	Sex	Age in years (at treatment initiation)	Age at UC Diagnosis	Duration of UC (at treatment initiation)	Montreal Classification	History of C. difficile	History of CMV colitis	Smoking status	Treatment ever received	Surgical history	Concomitant treatment
1	f	44.2	38.6	5.7	E2	No	No	Never	5-ASA (oral and rectal), Budesonide (oral and rectal), systemic steroids, Entocort, Hydrocortisone (rectal)	None	None
2	m	36.3	23.7	12.7	E2	No	No	Past	5-ASA (oral and rectal), Budesonide (oral and rectal), systemic steroids, Ciprofloxacin, AZA (10/2008-12/2011), Lecithin, rectal prednisolone and cinchocain.	None	Systemic steroids during the first 2 weeks
3	m	21.2	7.5	13.8	E1	No	No	Never	Ipecacuanha, 5-ASA (oral and rectal), systemic steroids, Budesonide (rectal), Metronidazole	None	None
4	m	17.0	15.5	1.5	E1	No	No	Never	Budesonide (rectal), 5-ASA (oral and rectal), systemic steroids, Blueberries, Ginkgo, Chia Seed, hempseed oil (oral)	None	None
5	f	37.0	22.5	14.5	E2	No	Yes	Never	5-ASA (oral and rectal), systemic steroids, metronidazole, ciclosporin, AZA, Budesonide (oral), valaciclovir, rectal prednisolone	None	5-ASA and AZA ongoing, systemic steroids during the first 2 weeks
6	f	46.0	33.2	12.8	E2	No	No	Never	5-ASA (oral and rectal), Budesonide (rectal), systemic steroids	None	5-ASA and Budesonide ongoing
7	f	30.6	25.0	5.6	E1	No	No	Never	Systemic steroids, AZA, Budesonide (rectal), 5-ASA (rectal)	None	None
8	f	28.5	25.7	2.8	E2	No	No	Never	Budesonide (rectal), 5-ASA (rectal), rectal prednisolon and cinchocain.	None	None
9	N.A.	69.0	N.A.	N.A.	E1	No	No	N.A.	N.A.	None	None

10	m	67.5	59.0	8.5	E1	No	No	Past	AZA, MTX, anti-TNF (2x)	Left-sided hemicolectomy due to sigma perforation	5-ASA (oral and rectal) ongoing
11	m	34.0	22.1	11.8	E2	No	No	Past	5-ASA, AZA, anti-TNF (3x)	None	5-ASA (oral), AZA and anti-TNF ongoing
12	m	69.5	54.8	14.8	E2	No	No	Past	AZA, systemic steroids, budesonide, anti-TNF (1x)	None	Anti-TNF ongoing

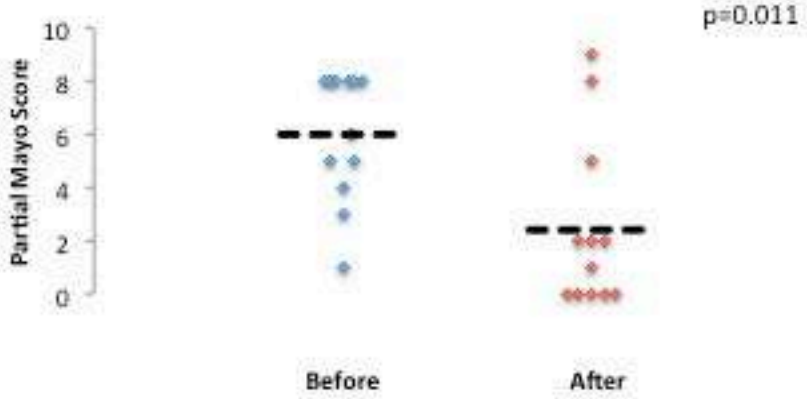
Supplementary Table 1: Patient demographics and past medical history. 5-ASA, mesalazine; AZA, azathioprine; C, Clostridium; MTX, methotrexate; UC, ulcerative colitis

Nr	Sex	Age in years	Duration of treatment in weeks	Indication for treatment	Number of daily stools before treatment	Number of daily stools after treatment	Partial Mayo Score before treatment	Partial Mayo Score after treatment	6-point symptom scale pre treatment	6-point symptom scale after treatment	FC before treatment (µg/g)	FC after treatment (µg/g)	Endoscopy before treatment	Endoscopy after treatment	Durability of Response (weeks)	Improvement	Relapse	ADE
1	f	44.2	6	Patient did not want systemic therapy	10	1.5	8	1	5	1	1110	16	3	NA	112	Yes	Yes	No
2	m	36.3	6	Malcompliance, patient did not want AZA	*5.5*	*1*	*8*	*0*	5	0	*401*	NA	*3*	2	*18*	*Yes*	*Yes*	No
3	m	21.2	6	Patient did not want systemic therapy	3	1	5	0	3	0	743	16	3	NA	73+	Yes	No	No
4	m	17.0	6	Patient did not want systemic therapy	1	1	1	0	0	0	116	9	3	0	69+	Yes	No	No
5	f	37.0	6	Severe disease course despite 5-ASA, topical steroids and AZA	8	1	8	0	5	0	498	328	3	NA	8	Yes	Yes	No
6	f	46.0	6	Patient did not want systemic therapy	6	3	8	2	5	1	351	NA	3	NA	1	Yes	Yes	No
7	f	30.6	6	Patient did not want systemic therapy	8	8	8	8	5	5	NA	NA	3	3		No		No
8	f	28.5	6	Patient did not tolerate 5-ASA, pregnancy	2	1	3	0	2	0	360	NA	1	3	1	Yes	Yes	No
9	NA	NA	6	NA	8	4.5	5	2	3	1	NA	NA	2	1	NA	Yes	Yes	No
10	m	67.5	6	Patient did not want systemic	3	2	4	2	2	1	337	506.3	3	NA	36	Yes	No	No

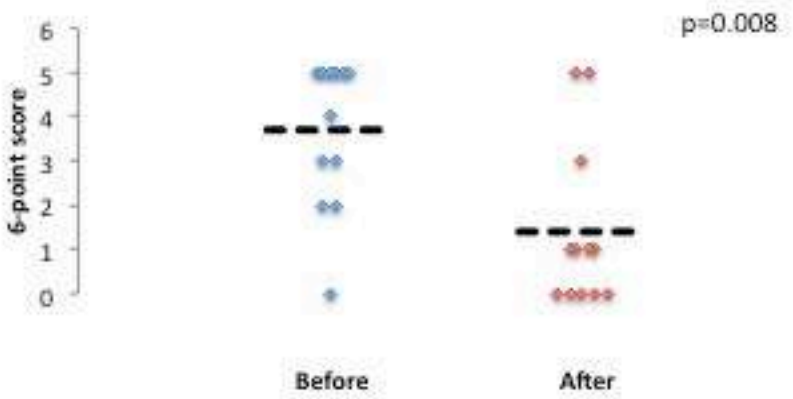
				therapy														
11	m	34.0	6	Left-sided colitis prior to anti-TNF	10	4	8	5	5	3	NA	NA	2	2	4	Yes	Yes	No
12	m	69.5	5	Left-sided colitis prior to anti-TNF switch	10	20	6	9	4	5	443.5	314.4	2	2		No		No

Supplementary Table 2: Response to Alicaforsen treatment. ADE, adverse drug events; 5-ASA, mesalazine; AZA, azathioprine; FC, fecal calprotectin

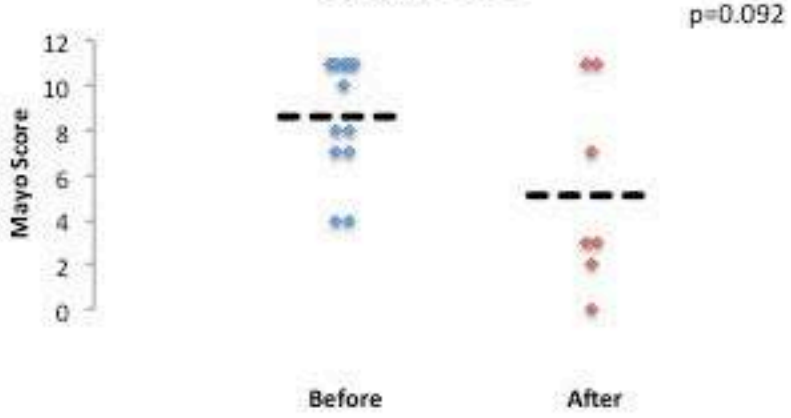
Partial Mayo Score before vs. after treatment



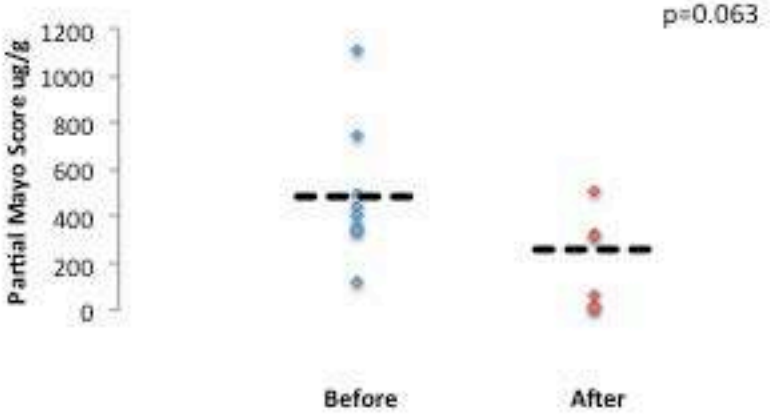
6-point score before vs. after treatment

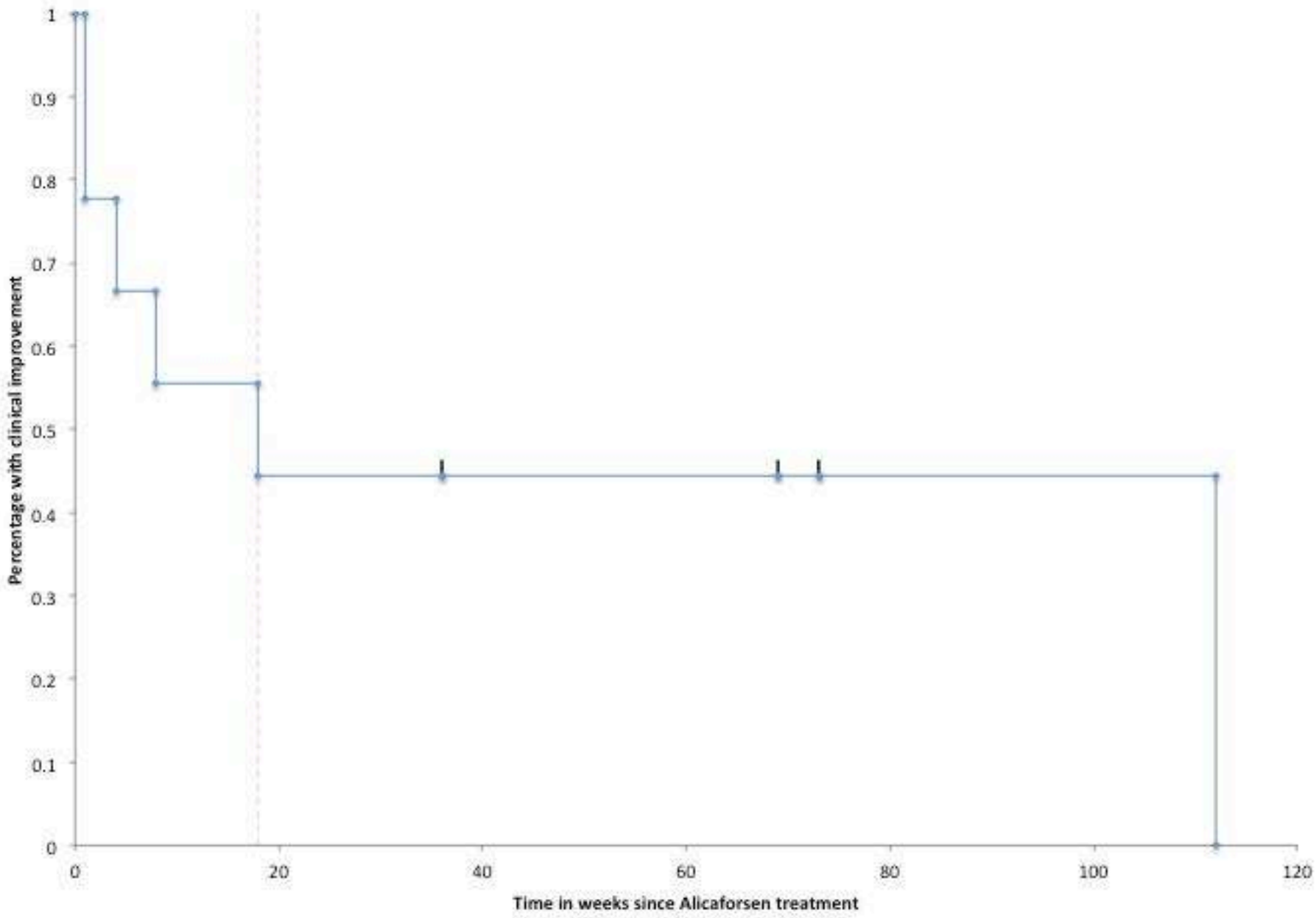


Mayo Score before vs. after treatment



Fecal Calprotectin before vs. after treatment




Patients with clinical improvement
Percentage with clinical improvement
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
20
40
60
80
100
120
Time in weeks since Alicaforsen treatment